Remarks

Claims 1 and 11-14 are currently pending. Claims 1 and 11-12 stand rejected under 35 U.S.C. § 112, first paragraph.

Applicants have cancelled claims 13 and 14 without prejudice to continued prosecution. Applicants have amended claim 1 to correct a minor grammatical informality. No new matter has been added.

Applicants respectfully request reconsideration and allowance of claims 1, 11, and 12 in view of the following remarks.

Withdrawal of Claims from Consideration

The Examiner has withdrawn claims 13 and 14 from consideration, citing the claims as being directed to a non-elected invention. Applicants respectfully disagree with the withdrawal of claims 13 and 14 from consideration. However, to expedite prosecution of the application, Applicants have cancelled claims 13 and 14 without prejudice to continued prosecution.

Rejection of Claims 1, 11, and 12 under 35 U.S.C. § 112, First Paragraph

Claims 1, 11, and 12 stand rejected under 35 U.S.C. § 112, first paragraph for lack of enablement. The Examiner states that a biological activity of treating viral hemorrhagic fever with the zymogen cannot be extrapolated from activated protein C, and the lack of a working example is problematic because the invention is directed to human therapy. The Examiner further states that "protein C" as used in the disclosure means the activated form and does not include the zymogen. Applicants respectfully disagree with this rejection.

At the outset, Applicants respectfully submit that the Examiner has not met his initial burden to establish a reasonable basis on which to question enablement. The Examiner's focus in the enablement rejection is that "protein C" as used in the application is limited to activated protein C; thus the teachings of the application only relate to the activated form. The Examiner also states the lack of a working example is problematic because the standard of enablement is somehow higher for methods of treating humans. However, the focus of the enablement requirement is to teach a person skilled in the art how to make and use the claimed invention. See M.P.E.P. § 2164. The test of enablement is whether the making and use of the claimed invention can be accomplished based on the art and the Applicant's specification without undue experimentation. See M.P.E.P. § 2164.01; *In re Wands*, 858

F.2d 731, 737, 8 U.S.P.Q. 2d 1400, 1404 (Fed. Cir. 1988).

Applicants are claiming the use of the protein C zymogen to treat viral hemorrhagic fever. The specification discloses how to make protein C zymogen (see Preparation 1 at p. 10 of the specification) and relevant dose ranges for treating patients in the clinic at page 8, lines 13-23 of the specification. Applicants have thus satisfied the enablement requirement.

The Examiner has not provided any evidence or arguments directed to information that is missing and/or why one skilled in the art could not supply this information without undue experimentation. See M.P.E.P. § 2164.04. Rather, the Examiner has asserted that because the zymogen form of protein C is inactive, it cannot be used to treat the conditions encompassed by the present invention. The Examiner notes that enzymatic activity is missing in the zymogen, and thus "there is no way to extrapolate a biological activity to the biologically inactive zymogen."

Applicants agree that the unprocessed zymogen is inactive. However, Applicants respectfully disagree with the Examiner's statement that the zymogen cannot be converted into its activated form in vivo after being administered in accordance with the teachings in the specification and the art, as detailed below. The Examiner's general disbelief that the invention will not work as claimed is not sufficient to support an enablement rejection. There must be reason to doubt the objective truth of the statements contained within the specification, which includes the claims, and an explanation as to why the Examiner does not believe the statements which the Applicants have set forth in the specification. See M.P.E.P. § 2164.04. In his rejection, the Examiner has merely stated that the slow conversion rate in vivo prevents the compound from being efficacious, relying on the rate of activation *in vivo* as discussed in Bang *et al.* (U.S. 5,151,268). Nothing in Bang *et al.* supports an assertion that a slow conversion rate to activated protein C is equated with no efficacy.

In drawing this conclusion, the Examiner has not recognized that a precursor, such as the protein C zymogen, can be an effective pharmaceutical agent by virtue of being converted (as would a pro-drug) to the active agent *in vivo*. The conversion of human protein C zymogen to activated protein C by limited proteolysis with thrombin in complex with thrombomodulin, as taught in the specification at page 1, lines 15-20, is known in the art.

Applicants respectfully submit that viral hemorrhagic fever is a hypercoagulable state (as stated at page 4, lines 11-13 of the specification), and that during such a state there is increased thrombin generation and thereby elevated activation of protein C. There are several examples in the art that document a positive correlation between the amount of thrombin generation in humans and the activation of protein C. For example, this correlation has been

observed in the hypercoagulable states of acute myocardial infarction (AMI) and sepsis.

In a study of thrombolytic therapy of patients with AMI, a significant positive correlation between plasma APC and thrombin generation in patients was observed (see right column, p. 43, and last sentence of right column, p. 44 of Takazoe *et al.*, Thromb. Res. 95:37-47, 1999). In another study, the effects of thrombin activity was examined following cessation of heparin therapy in patients with acute coronary syndromes (two-thirds of the syndromes were AMI). In that study, a transient increase in thrombin activity was accompanied by a correlative increase in activation of protein C (see middle paragraph, left column p. 1934 in Granger *et al.*, Circ. 91:1929-1935, 1995).

A similar correlation between thrombin levels and activation of protein C has been observed in patients with sepsis. For example, patients with neutropenia who developed septic shock were found to have increased thrombin generation (see second full paragraph, left column, p. 885 of Mesters *et al.*, Blood 88:881-886, 1996). Further analysis of samples from these patients indicated that the increased thrombin generation of the hypercoagulable state correlated with activation of protein C (see first full paragraph, left column, p. 2213 of Mesters *et al.*, Crit. Care Med. 28:2209-2216, 2000). The correlation of thrombin levels and activated protein C levels was also observed in a study of children with severe meningococcal sepsis who were treated with protein C. In that study, a close correlation of thrombin and activated protein C levels was observed both prior to and during treatment with protein C (see last paragraph, right column, p. 1844 of de Kleijn *et al.*, Crit. Care Med. 31:1839-1847, 2003).

Furthermore, treatment with the zymogen is known in the art, as evidenced by its use in the treatment of severe sepsis. Several case reports or small clinical studies have been conducted using human protein C zymogen. For example, protein C zymogen was used to treat purpura fulminans associated with intravascular coagulation in a 13-year-old patient (see Gerson *et al.*, Pediatrics 91:418-422, 1993). In another clinical study, four children requiring intensive treatment for meningococcemia with shock, disseminated intravascular coagulation, and purpura fulminans were administered protein C zymogen (see Rivard *et al.*, J. Pediatr. 126:646-652, 1995). Each of these children had a rise in plasma C levels to near normal levels. Yet another example of administration of protein C zymogen resulting in restoration of normal plasma protein C levels is provided in a case study of three adult patients in the treatment of coagulopathy in meningococcal disease (see Rintala *et al.*, Crit. Care Med. 26:965-968, 1998).

These examples demonstrate that increased levels of thrombin in a hypercoagulable state will be accompanied by a correlation of increased activation of protein C. Accordingly, one of skill in the art would have a reasonable expectation that administration of human protein C zymogen to a patient with viral hemorrhagic fever would provide therapeutic effectiveness.

In addition to the use of human protein C zymogen in the above-cited and other case studies, Applicants respectfully submit that protein C zymogen has been approved for use by the European Agency for the Evaluation of Medicinal Products (EMEA). Human protein C was authorized for marketing in the European Union on July 16, 2001 for the treatment of purpura fulminans and coumarin-induced skin necrosis in patients with severe congenital protein C deficiency (see EMEA CEPROTIN abstract). This approval, coupled with case studies documenting treatment with protein C, demonstrate acceptance of use of human protein C zymogen as a therapeutic agent in the art.

In his enablement rejection, the Examiner concludes that the lack of a working example is a real problem with respect to the present invention, stating that the standard of enablement is higher for inventions targeted for human therapy because effective treatments for disease conditions are relatively rare. Applicants respectfully submit this statement has been made without substantiation and that it improperly asserts methods of treating a human are somehow held to a higher standard of enablement.

Moreover, the presence of a working example is but one of many factors to be considered in the determination of whether any experimentation is undue. *In re Wands*, 858 F.2d 731, 737, 8 U.S.P.Q. 2d 1400, 1404 (Fed. Cir. 1988). The specification need not contain an example if the invention is otherwise disclosed such that one of skill in the art will be able to practice it without undue experimentation. See M.P.E.P. 2164.02; *In re Borkowski*, 422 F.2d 904, 908, 164 U.S.P.Q. 642, 645 (CCPA 1970). Applicants respectfully submit that in consideration of other factors, the claimed invention is enabled. The specification is commensurate with the breadth of the claims, which are focussed on treatment of viral hemorrhagic fever with protein C zymogen. In considering the state of the prior art and the level of skill in the art, there is a working example with respect to how to make the zymogen (see Preparation 1, page 10) and direction regarding route and dose for administration (page 8, lines 13-23). Thus, the specification enables one of skill in the art to practice the claimed invention.

The Examiner states that the clear cumulative conclusion is that "protein C" as used in the application means activated protein C, and does not include or mean the zymogen. Applicants respectfully disagree, as the intention to include the zymogen within the scope of the invention is evident in the claims as initially filed in the parent application. Original claim 1 encompassed use of protein C to treat viral hemorrhagic fever, from which dependent claim 2 specified the zymogen.

The inclusion of the zymogen in the use of the term "protein C" is further evident in the discussion of administering compositions comprising protein C at page 8, lines 17-26 of the specification. The amount of protein C administered is stated as generally from about 5.0 to about 250 μg/kg/hr. Use of aPC is stated to be preferred, with the amount of aPC administered from about 1.0 to about 96 μg/kg/hr, not up to about 250 μg/kg/hr. The general administration amount up to about 250 μg/kg/hr thereby encompasses use of the zymogen since this amount is greater than the upper administration limit of 96 μg/kg/hr for aPC.

The intention to include the zymogen within the meaning of protein C is further supported by the terminology of the specification. At page 5, line 5, the specification states "Protein C includes and is preferably human protein C. . . ." Human protein C is defined as "human protein C zymogen" (page 5, line 26). At page 10, Preparation 1, "Preparation of Human Protein C" describes production of recombinant human protein C zymogen. In describing formulations of protein C, the specification states use of "protein C or aPC" at page 8, lines 11-12, further indicating that "protein C" includes the zymogen and is not limited to aPC.

In view of the above, Applicants respectfully submit that the term "protein C" includes the zymogen and that its use in the methods of the claimed invention have been enabled. Accordingly, Applicants request withdrawal of the rejection under 35 U.S.C. § 112, first paragraph.

Conclusion

Having addressed all outstanding issues, Applicants respectfully request entry and consideration of the foregoing amendments and reconsideration and allowance of the case.

To the extent the Examiner believes that it would facilitate allowance of the case, the Examiner is invited to telephone the undersigned at the number below.

Respectfully submitted,

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